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This training grant for 5 predoctoral students was designed to integrate students in diverse disciplines with a common interest in understanding breast cancer. The training features of this program were 1) a monthly journal club to facilitate the exchange of current information related to breast cancer research, 2) participation in a yearly retreat to encourage interactions between trainees and investigators at Vanderbilt University interested in Breast Cancer research, and 3) a special seminar involving a guest speaker prominent in the field of breast cancer research. Twelve individual students were supported throughout the four year funding period, and this work resulted in 22 publications or submitted manuscripts that were supported at least in part by this program. Two students have received Ph.D. degrees, one a M.D./Ph.D. degree, and two M.S. degrees. The remaining students are still matriculated in Ph.D. or M.D./Ph.D. programs. The research performed was highly focused on topics relevant to cancer research, for example growth factor regulation and processing, cell:cell interactions, and oncogene signalling pathways, as well as topics directly related to breast cancer, including estrogen receptor regulation, mammary gland development, and polymorphisms associated with breast cancer risk. The program has therefore met the goal of training investigators for careers in breast cancer research.

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FOREWORD

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FINAL REPORT
ARMY BREAST CANCER TRAINING GRANT DAMD17-94-J-4024

INTRODUCTION:

This training grant for 5 predoctoral students/year was designed to integrate students in diverse disciplines with a common interest in understanding breast cancer. The special features of the training grant were a monthly journal club, a yearly retreat, and the invitation of a seminar speaker prominent in the field of breast cancer research. These mechanisms were designed to provide students with opportunities to enhance their own research by stimulating communication with investigators at Vanderbilt interested in Breast Cancer research, increasing their knowledge of current literature in the field, and exposing them to the latest research from prominent investigators at other institutions. Trainees were required to successfully complete the Cancer Biology course (4 credits, CBIO 342). Progress is measured by the presentation of original research in the form of abstracts and publishable manuscripts.

PROGRESS:

Students:

The following table summarizes the students supported by the Breast Cancer Training Grant (BCTG) over the four-year funding period for the grant. Their name, departmental affiliation, and years supported by the training grant are indicated. In addition, if the student has received an advanced degree from Vanderbilt University by the time of this final report, that degree is indicated. Two of the three students who have received Ph.D. degrees are currently postdoctoral fellows in highly-respected cancer biology laboratories. The third student, Dr. Renee Bailey, is pursuing additional training in Biostatistics and is planning a career in population-based research dealing specifically with breast cancer. Two students received M.S. degrees and are pursuing teaching careers. All students listed who have not yet received degrees are still matriculated in the Ph.D. or M.D./Ph.D. (M.S.T.P.) Program.

NAME	DEPT	yr1	yr2	yr3	yr4	
Mark Alexandrow	Cell Biology	X				Ph.D.
Renee Bailey	Pathology	X	X	X	X	Ph.D.
Mike Engel	M.S.T.P./Cell Biology	X				
Laura Niedernhofer	M.S.T.P./Biochemistry	X	X			M.D. /Ph.D
Cindy Yee	Pathology	X	X	X		
Heather Joseph	Cell Biology		X	X		M.S.
Suzanne Szak	Biochemistry		X	X		
Rebecca Townsend	Cell Biology			X		M.S.
Christa Brown	Cell Biology				X	
Paul Ruest	Cell Biology				X	
Molly Thoreson	Cell Biology				X	
Tracy Vargo-Gogola	Cell Biology				X	

The Progress of each student supported by the Breast Cancer Training Grant is measured by presentation of abstracts at national meetings and publications. The following is a list of publications produced by each student which represent work performed, at least in part, during their tenure on the BCTG. In addition, abstracts presented during the time they were funded by the BCTG are listed. In the case of several first year students who were supported for a limited time on this grant, their research accomplishments thus far are presented in paragraph form.

Mark Alexandrow

Alexandrow, M.G. and H.L. Moses, "Late-G1 effects of c-myc on TGFβ1-induced inhibition of mouse keratinocytes". Abstract presented at Keystone Symposium "Oncogenes: 20 years later", 1995.

Alexandrow MG, Kawabata M, Aakre M, Moses HL. Overexpression of the c-myc oncoprotein blocks the growth-inhibitory response but is required for the mitogenic effects of transforming growth factor beta 1. Proceedings of the National Academy of Sciences of the United States of America 92(8):3239-43, 1995

Alexandrow M, Moses HL.Transforming growth factor beta and cell cycle regulation. Cancer Research 55(7):1452-7, 1995

Alexandrow MG, Moses HL. Kips off to Myc: implications for TGF beta signaling. Journal of Cellular Biochemistry 66(4):427-32, 1997

Renee Bailey

Bailey, L.R., Roodi, N., Haines, J.L., Dupont, W.D., and Parl, F.F. Evidence for association of the estrogen receptor gene with familial breast cancer. Submitted to Journal of the National Cancer Institute, June 1998.

Bailey, L.R., Roodi, N., Dupont, W.D. and Parl, F.F. Association of cytochrome P450 1B1 (CYP1B1) polymorphism with steroid receptor status in breast cancer. Submitted to Cancer Research, June 1998.

Bailey, L.R., Roodi, N., Verrier, C.S., Dupont, W.D., and Parl, F.F. Breast cancer and CYP1A1, GSTT1 polymorphisms: evidence of a lack of association in Caucasians and African Americans. Cancer Research, 58(1): 65-70, 1998. (Also presented as Abstract in the Proceedings of the American Assoc. For Cancer Research, 1997).

Verrier, C.S. Roodi, N. Yee, C.J., Bailey, L.R., Jensen, R.A., Bustin, M., and Parl, F.F. High-mobility group (HMG) protein HMG-2 and TATA-binding protein-associated factor TAF(II)30 affect estrogen receptor-mediated transcriptional activation. Molecular Endocrinology, 11(8): 1009-19, 1997. (Also presented as Abstract at the Endocrine Society meeting, 1997)

Roodi, N., Bailey, L.R., Kao, W.Y., Verrier, C.S., Yee, C.J., Dupont, W.D., and Parl, F.F. Estrogen receptor gene analysis in estrogen receptor-positive and receptor-negative primary breast cancer. Journal of the National Cancer Institute, 87(6): 446-51, 1995.

Yaich, L.E., Roodi, N., Bailey, L.R., Verrier, C.S., Yee, C.J., Cavener, D.R. and Parl, F.F. Analysis of the estrogen receptor (ER) gene, transcript, and protein in ER-positive and -negative breast cancer cell lines. Endocrine-Related Cancer, 2(4): 293-309, 1995

Meetings:

Presentation as a New Investigator at the Era of Hope Breast Cancer Meeting, October 1997.

Mike Engel

Kawabata M, Imamura T, Miyazono K, Engel ME, Moses HL.
Interaction of the transforming growth factor-beta type I receptor with farnesyl-protein transferase-alpha. Journal of Biological Chemistry 270(50):29628-31, 1995.

Engle, M.E., Datta, P.K., and Moses, H.L. RhoB is stabilized by TGF-beta and antagonizes transcriptional activation. Journal of Biological Chemistry 273: 9921-9926, 1998.

Laura Niedernhofer

Niedernhofer LJ, Riley M, Schnetz-Boutaud N, Sanduwaran G, Chaudhary AK, Reddy GR, Marnett LJ. Temperature-dependent formation of a conjugate between tris(hydroxymethyl) aminomethane buffer and the malondialdehyde-DNA adduct pyrimidopurinone. Chemical Research in Toxicology 1997 May;10(5):556-61

Niedernhofer, L.J., Rouzer, C.A., Greene, R.E., and Marnett, L.J. Mutagenicity of the endogenous metabolite malondialdehye in human cells: induction of deletions and GC-AT transitions via interstrand crosslinks. Submitted

Niedernhofer, L.J., Chaudhary, A.J., and Marnett, L.J. "Mutagenicity of Malondialdehyde in Human Cells". Eighth International Conference on Carcinogenesis and Risk Assessment, 1995

Cindy Yee

Yee, C.J., N. Roodi, C.S. Verrier, and F.F. Parl. "Microsatellite instability and loss of heterozygosity in breast cancer". Cancer Res. 54: 1641-1644, 1994.

Yee, C.J., C.S. Verrier, L.R. Bailey, N. Roodi, and F.F. Parl, "Molecular characterization of lobular breast cancer". Abstract presented at the 86th Annual Meeting of the American Association for Cancer Research, Toronto, Canada

Verrier, C.S. Roodi, N. Yee, C.J., Bailey, L.R., Jensen, R.A., Bustin, M., and Parl, F.F. High-mobility group (HMG) protein HMG-2 and TATA-binding protein-associated factor TAF(II)30 affect estrogen receptor-mediated transcriptional activation. Molecular Endocrinology, 11(8): 1009-19, 1997.

Roodi, N., Bailey, L.R., Kao, W.Y., Verrier, C.S., Yee, C.J., Dupont, W.D., and Parl, F.F. Estrogen receptor gene analysis in estrogen receptor-positive and receptor-negative primary breast cancer. Journal of the National Cancer Institute, 87(6): 446-51, 1995.

Yaich, L.E., Roodi, N., Bailey, L.R., Verrier, C.S., Yee, C.J., Cavener, D.R. and Parl, F.F. Analysis of the estrogen receptor (ER) gene, transcript, and protein in ER-positive and -negative breast cancer cell lines. Endocrine-Related Cancer, 2(4): 293-309, 1995

Heather Joseph

Gorska, A.E., Joseph, H., Derynck, R., Moses, H.L., and Serra, R. Targeted expression of a dominant negative TGF-beta type II receptor to the mammary gland results in alveolar hyperplasia and beta-casein expression in virgin mice. Cell Growth Differ. 9: 229-238, 1998.

Suzanne Szak

Szak, S.T., and Pietenpol, J.A. High Affinity Insertion/Deletion Lesion Binding by p53: Evidence for a Role of the p53 Central Domain". Submitted.

Rebecca Townsend
Rebecca was supported for her first year as a Cell Biology graduate student by this training mechanism. Her project involved generating transgenic mice containing a naturally occuring splice variant of the human BRCA1 gene under the control of the mouse mammary tumor virus (MMTV) promoter/enhancer, which directs expression to the mammary gland. Expression of this human BRCA1 splice variant results in a hyperplasia of the ductal system, which is opposite of the effect of other tumor suppressors on the mouse mammary gland.

Christa Brown
Brown, C.L., Meise, K.S., Bogatcheva, G., Dempsey, P.J., and Coffey, R.J. High MW 44kDa amphiregulin is the predominant form released by metalloprotease inhibitor-sensitive processing of the human AR precursor. Abstract, Mol. Biol. of the Cell, A.S.C.B. meeting, 1997.

Brown, C.L., Meise, K.S., Plowman, G.D., Coffey, R.J., and Dempsey, P.J. 1998. Cell surface ectodomain cleavage of human amphiregulin precursor is sensitive to a metalloprotease inhibitor. J. Biol. Chem. In press

Vecchi, M., Rudolph-Owen, L.A., Brown, C.L., Dempsey, P.J., and Carpenter, G. 1998. Tyrosine phosphorylation and proteolysis: pervanadate-induced, metalloprotease-dependent cleavage of the erbB4 receptor and amphiregulin. J. Biol. Chem. In press.

Molly Thoreson
Wu, J., Mariner, D.J., Thoreson, M.A., and Reynolds, A.B. 1998. Production and characterization of monoclonal antibodies to the catenin p120ctn. Hybridoma 17. 175-183.

Thoreson, M.A., Hummingbird, D., and Reynolds, A.B. Role of the p120ctn interaction with E-cadherin. Mol. Biol. of the Cell, A.S.C.B. abstracts, 1997.

Paul Ruest
Paul Ruest is a first year Cell Biology graduate student supported to investigate the mechanism by which focal adhesion kinase contributes to cell invasion and metastasis. He is currently investigating the mechanisms by which the protooncogene Src and FAK cooperate to mediate the phosphorylation of p130Cas, a protein present in focal adhesions. Cas has been reported to be a positive effector of cell migration. His studies have revealed that Fak activation loop phosphorylation is a critical step leading to efficient autophosphorylation and signalling, and that recruitment of Src to the FAK autophosphorylation site is a key step leading to Cas phosphorylation.

Tracy Vargo-Gogola
Tracy is a first year Cell Biology graduate student supported to investigate the expression of the metalloproteinase matrilysin in breast cancer cells and the role it plays in tumor progression. The expression of matrilysin in the mammary gland of transgenic mice results in accelerated development of tumors induced by the oncogene neu. Matrilysin is expressed in MDA MB468

cells but not in "normal" HBL100 breast cells. One difference between these cell lines is the absence of alpha-catenin in MDA MB468 cells. Restoring alpha-catenin by fusion with HBL 100 cells, or by direct transfection of alpha-catenin expression construct, results in a reduction in matrilysin levels. The possibility that modulation of the actin cytoskeleton and cell:cell interactions are responsible for the induction of matrilysin is being investigated.

Journal Club

The Breast Cancer Journal/Research Club has met the first Tuesday of every month at 5:00 for the duration of the funding period of this grant. All students supported by the grant were required to attend, and the sessions were also attended by faculty, post-doctoral fellows, residents, and other students interested in breast cancer research. The format varied and included presentations by students, faculty, and outside guest speakers. In particular, an attempt to provide basic and more advanced talks on topics such as the early detection of breast cancer, current treatments for breast cancer, and diagnosis of malignant and premalignant disease was made by inviting investigators from the departments of Surgery, Radiology, Oncology, and Pathology to present in this format. This forum provided the opportunity for informal discussions and interactions between individuals with a varied scientific background and served the purpose of expanding the interest and interaction of the students to more diverse areas, including in clinical arenas.

Retreat

A Breast Cancer Program retreat was held the first two years of the grant period. At that time, the institution of a Vanderbilt Cancer Center-wide retreat and changes in the leadership of the Breast Cancer Program resulted in the incorporation of the annual retreat into the VCC retreat. Students supported by the training grant actively participated in both forums, presenting posters and interacting with other Breast Cancer Program and VCC members.

Seminar speakers

Seminar speakers with a specific interest in Breast Cancer were invited each year of the retreat. Students supported by the training grant attended the seminar and then had time for informal interactions with the speaker over lunch. The speakers supported for the four years of this grant were Dr. William Muller of McMaster Univ., Dr. Mary Claire King of the Univ. of Washington, Dr. Allen Oliff of Merck Pharmaceuticals, and Dr. Malcolm Pike of U.S.C.

CONCLUSIONS

The Breast Cancer Training Grant has supported 5 predoctoral students for each of the four years of support. Research productivity of each student has been excellent, with a total of 22 publications or submitted manuscripts and many abstracts attributed to work carried out with the support of this training mechanism. The research has been in most cases highly focused on breast

cancer, including topics on estrogen receptor regulation, mammary gland development, and cytochrome polymorphisms as they relate to breast cancer risk. In other cases, basic cancer research problems of considerable relevance to breast cancer were addressed, including studies on growth factor regulation and processing, cell:cell interactions, and oncogene signalling pathways. Students have had the opportunity to interact on a regular basis with faculty and others interested in breast cancer through the monthly Breast Cancer Journal Club. This forum has been particularly helpful in exposing these students to the clinical aspects of breast cancer research and allowing them the opportunity to interact with surgeons, oncologists, radiologists, and pathologists involved in the treatment of breast cancer patients. The exposure to outside speakers who are well known in the field of breast cancer research, including Drs. Mary Claire King and Malcolm Pike, provided the opportunity to hear the latest information in the field and interact on a personal level with these distinguished investigators. These students either have or will receive advanced degrees and are pursuing careers related specifically to cancer research, and in most cases, directly to breast cancer research. This training program has therefore been successful in meeting its goals of training the next generation of investigators interested in this disease.

REFERENCES: NA

APPENDICES: NA